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PMRA Sub. No. 2004-0789/DOW AMINOPYRALID/AMD | ~ PROTECTED ~ | Mouse Carcinogenicity Study / 1 DACO 4.4.3 / OECD IIA 5.5.3

PMRA Primary Reviewer: Brenda MacDonald, DVM
Fungicide/Herbicide Toxicological Evaluation Section, Health Evaluation Division
Signature: for
Date Aug 31, 2005

EPA Secondary Reviewer: Karlyn J. Bailey, M.S.
Registration Action Branch 2, Health Effects Division (7509C)
Signature:
Date 9/1/05

TXR#: 0053657

DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity Feeding Study in Mice; OPPTS 870.4200; OECD 451.

PC CODE: 005100 **DP BARCODE:** D305670

TEST MATERIAL (PURITY): XDE-750, purity 94.5% (3,6-dichloro-4-amino-2-pyridinecarboxylic acid).

SYNONYMS: Aminopyralid; XR-750; X660750.

CITATION: Stebbins K.E., et al (2003) XDE-750: Oncogenicity Dietary Study in CD-1 Mice. Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Laboratory Project Study ID 011163, December 19, 2003. Unpublished.

SPONSOR: Dow Agrosciences LLC, Indianapolis, Indiana.

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 46235628), purity 94.5%, was administered to 50 CD-1 mice/sex/dose in the diet at dose levels of 0, 50, 250 or 1000 mg/kg bw/day (equal to 0, 50.2, 251 or 1000 mg/kg bw/day for males, and 0, 50.9, 252 or 1010 mg/kg bw/day for females) for 18 months.

There were no treatment-related effects on mortality, clinical signs, ophthalmology, body weight/body weight gain, food intake, food efficiency, hematology, organ weights, gross pathology or histopathological examination. The only oncogenic finding was an increased incidence of pulmonary bronchiolo-alveolar carcinomas in the 1000 mg/kg bw/day group, males only. Historical control data for this tumour type indicated that the incidence observed in this study was within the normal range. Thus the slight increased in bronchiolo-alveolar tumours in the high-dose males was not considered to be treatment related.

The systemic LOAEL could not be determined since there were no adverse, treatment-related findings. The NOAEL is 1000 mg/kg bw/day (equal to 1000 mg/kg bw/day for males and 1010 mg/kg bw/day for females).

This carcinogenicity study in the mouse is acceptable and satisfies the guideline requirement for a carcinogenicity study (OPPTS 870.4200); OECD 451 in mice.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** XDE-750

Description:	Technical; tan powder.
Lot/Batch #:	F-0031-125; TSN102095
Purity:	95.4% a.i.
Compound Stability:	Not stated.
CAS #:	150114-71-9

2. **Vehicle:** Test material was mixed with control diet (Purina #5002 Certified Rodent Lab Diet).

3. **Test Animals:**

Species:	Mouse	
Strain:	CD-1	
Age/weight at study initiation:	6 weeks of age; Males, 27.2 g to 33.9 g; Females, 20.8 g to 27.7 g.	
Source:	Charles River Laboratories, Inc., Portage, MI.	
Housing:	Individually housed in suspended stainless steel cages with wire-mesh floors.	
Diet:	Purina Certified Rodent Lab Diet #5002 in meal form, *ad libitum*	
Water:	Municiple water, *ad libitum*	
Environmental conditions:	**Temperature:**	21.6-22.2°C
	Humidity:	44.9-62.1%
	Air changes:	12-15/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	7 days.	

B. STUDY DESIGN:

1. **In Life Dates:** November 14, 2001 to May 20, 2003.

2. **Animal Assignment/Dose Levels:** Animals were stratified by body weight and then randomly assigned using a computer program to the test groups noted in Table 1.

TABLE 1 - Study Design

Test Group	Conc. in Diet (mg/kg bw/day)	Dose to Animal (mg/kg bw/day)	# Males	# Females
Control	0	0/0	50	50
Low	50	50.2/50.9	50	50
Mid	250	251/252	50	50
High	1000	1000/1010	50	50

3. **Dose Selection:** The limit test of 1000 mg/kg bw/day was chosen as the high-dose based on the results of a 90-day mouse study in which adverse effects were not observed. The intermediate- and low-dose levels were expected to provide dose-response data for any treatment-related effect(s) observed in the high-dose group. The low dose was also expected to be a no-observed-effect level (NOEL).

4. Diet Preparation and Analysis: Diets were prepared by serially diluting a concentrated test material-feed mixture (premix) with ground feed. Premixes were mixed approximately bi-monthly for the first 90 days of the study, and at approximately monthly intervals thereafter. Initial concentrations of test material in the diet were calculated from historical control body weights and food consumption data. Subsequently, the concentrations of the test material in the feed were adjusted weekly for the first 90 days of the study and at approximately monthly intervals thereafter, based upon the most recent body weight and food consumption data. Stability of the test material in diet for up to 21 days was demonstrated in the 4-week dietary toxicity study in mice (MRID 46235624). Additional stability analyses were evaluated for at least 34 days at concentrations of 0.00258% and 5% (premix) to enable monthly mixing procedures. Homogeneity of mixing was determined for the low-dose female diets and high-dose male diets prior to study initiation and during months 3, 8, 13 and 17. Actual test material concentration in the diet was determined for all dose levels from test diets prepared just prior to study initiation and during months 3, 8, 13 and 17.

Results - Homogeneity Analysis: Individual samples of 5 separate batches of the 50 mg/kg bw/day female test diets ranged from 92.2% to 121.7%, 104.7% to 117.8%, 90.8% to 103.2%, 88.3% to 98.8% and 96.1% to 103.0% of the nominal concentration, respectively. Individual samples of 5 separate batches of the 1000 mg/kg bw/day male test diets ranged from 99.2% to 107.3%, 97.0% to 129.8%, 96.2% to 102.5%, 82.8% to 92.7% and 95.0% to 100.4% of the nominal concentration, respectively.

Stability Analysis: i) Results from the 4-week mouse dietary study, MRID 46235624. The actual concentration of XDE-750 in the 10 and 1000 mg/kg bw/day test diets, expressed as percentage of the nominal concentration, were as follows:

Dose (mg/kg bw/day)		
Storage Interval	**10**	**1000**
Day 0	95.6%	109.0%
Day 21	100.6%	116.8%

ii) Results from stability analysis conducted for the current study, at dose levels of 0.025% and 5%, expressed as percentage of the nominal concentration:

Dose (%)		
Storage Interval	**0.0258**	**5**
Day 0	80.6%	103.5%
Day 10	99.6%	83.2%
Day 23	109.7%	100.0%
Day 35	122.5%	84.6%

Concentration Analysis: The range of values for the actual concentrations of XDE-750 in the test diets, and the overall mean values, expressed as percentage of the nominal concentrations, were as follows:

	Dose (mg/kg bw/day)			
	0	50	250	1000
Actual concentration, ppm Range of values Mean value	None detected	45.3 to 62.5 53.3	241.3 to 290.0 263.8	857.0 to 1060.0 976.0
% of target concentration Range of values Mean value	None detected	90.5% to 125.0% 106.5%	96.5% to 116.0% 105.5%	85.7% to 106.0% 97.6%

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5.. **Statistics:** Means and standard deviations were calculated for all continuous data. Body weights, feed consumption, organ weights, and total white blood cell counts were evaluated by Bartlett's test for equality of variances (alpha = 0.01). Based on the outcome of Bartlett's test, exploratory data analysis was performed by a parametric or nonparametric analysis of variance (ANOVA). If the ANOVA was significant at alpha = 0.05, it was followed respectively by Dunnett's test or the Wilcoxon Rank-Sum test with a Bonferroni correction for multiple comparisons to the control. The experiment-wise alpha level of alpha = 0.05 was reported for Dunnett's test and Wilcoxon Rank-Sum test. DCO incidence scores were statistically analyzed by a z-test of proportions comparing each treated group to the control group at alpha = 0.05. Descriptive statistics only (means and standard deviations) were reported for body weight gains, feed efficiency, and differential WBC counts. Statistical outliers were identified by a sequential test (alpha = 0.02), but routinely excluded only from feed consumption and feed efficiency analyses. Outliers were excluded from other analyses only for documented, scientifically sound reasons.
Statistical analyses were conducted on body weight, feed consumption, and organ weight data throughout this oncogenicity study. However, such data near termination of an oncogenicity rodent study were confounded by a spectrum of geriatric changes, the presence of spontaneous tumors, secondary effects from tumors, and terminal changes prior to death. As a result of these changes, statistical tests were of questionable value and extra caution should be applied in interpreting the statistical result.
Gross pathologic observations were tabulated and considered in the interpretation of final histopathologic data, but were not evaluated statistically. The cumulative incidence of histopathologic observations for all animals scheduled for the terminal sacrifice was used in the statistical analysis. For tissues where all animals in all dose groups were scheduled to be examined, the incidences of specific histopathologic observations were first tested for deviation from linearity (alpha = 0.01) using ordinal spacing of the doses. If linearity was not rejected the data was then tested for a linear trend using the Cochran-Armitage Trend test. If the trend was statistically significant at alpha = 0.02, or if significant deviation from linearity was found, incidences for each dose group were compared to that of the control group using a pairwise Chi-square test with Yates' continuity correction (alpha = 0.05, two-sided). For tissues which were evaluated from all control-dose and high-dose animals, but only from selected animals in the intermediate-dose groups, statistical analysis consisted of the pairwise comparisons of control and high dose using the pairwise Chi-square test with Yates' continuity correction (alpha = 0.05, two-sided). Rare tumors, those with a background incidence of less than or equal to 1%, were considered significant in the Chi-square test with Yates' continuity correction at alpha = 0.10, two-sided. Differences in mortality patterns were tested by the Gehan-Wilcoxon procedure for all animals scheduled for terminal sacrifice. If a significant effect was identified for all dose groups (alpha = 0.05) then individual analyses were run comparing each dose to control and were Bonferroni corrected to compensate for the multiple

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comparisons with the control group. The experiment-wise alpha level was reported. Since there were statistically-identified differences in median survival times among the treatment groups for females, mortality adjusted analyses for tumors were used.

C. METHODS:

1. Observations: A cage-side examination was conducted at least once a day. This examination was performed with the animals in their cages and include, but were not limited to: activity, repetitive behavior, vocalization, incoordination/lameness, injury, neuromuscular function (convulsion, fasciculation, tremor, twitches), altered respiration, blue/pale skin and mucous membranes, severe eye injury (rupture), fecal consistency, and fecal/urinary quantity. At least twice daily, usually at the beginning and end of each day, all animals were observed for morbidity and mortality, and the availability of feed/water. Detailed clinical observations (DCO) were conducted on all animals on days 7 for females and 8 for males (baseline) and at approximately monthly intervals for months 1-9. During months 9-12, month 17 and at study termination, the first 10 surviving animals/sex/dose group were evaluated for DCO parameters. These examinations were performed at approximately the same time each examination day according to an established format, which included cage-side, hand-held and open-field observations that were recorded categorically or using explicitly defined scales (scored). Additionally, all animals were examined for palpable masses once per month, starting at month 6 and continuing through month 18. The time of onset, location, dimensions, appearance and progression of each palpable mass was recorded.

2. Body Weight: All mice were weighed during the pre-exposure period, weekly during the first 13 weeks of the study and then at approximately monthly intervals, thereafter.

3. Food Consumption and Compound Intake: Feed consumption data were collected weekly during the first 13 weeks of the study and then at approximately monthly intervals for all animals by weighing feed containers at the start and end of a measurement cycle. Mean daily dietary consumption was calculated as g food/kg body weight/day. Food efficiency (body weight gain in kg/food consumption in kg per unit time X 100) and compound intake (expressed as mg/kg bw/day and PPM) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. Ophthalmoscopic Examination: The eyes of all animals was examined by a veterinarian pre-exposure and prior to the scheduled necropsy using indirect ophthalmoscopy. Eyes were also examined by a prosector during the necropsy using a moistened glass slide pressed to the cornea.

5. Hematology: Blood smears were made from all surviving, non-fasted, animals, while under carbon dioxide anesthesia, via sample collection from the pedal vein (12 months) or orbital sinus at terminal sacrifice (18 months). Blood from moribund animals was obtained from the pedal vein or tail. Blood smears were not obtained from animals that died spontaneously. A white blood cell count and differential white blood count were determined from all animals in the treated and control groups at terminal sacrifice. A differential white blood cell count, as derived from the blood smears, was not determined from animals that were moribund due to the absence of effects at 18 months.

Clinical Chemistry: Not conducted.

6. Urinalysis: Not conducted.

7. Sacrifice and Pathology: At study termination, animals were anesthetized by inhalation of carbon dioxide, sacrificed by decapitation, and then necropsied. The CHECKED (✓) tissues were collected and preserved in neutral, phosphate-buffered 10% formalin, then prepared for histological examination. In addition, the (✓✓) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
✓	Oral tissues	✓	Aorta	✓	Brain
✓	Salivary glands	✓	Heart	✓	Periph.nerve
✓	Esophagus	✓	Bone marrow	✓	Spinal cord (3 levels)
✓	Stomach	✓	Lymph nodes	✓	Pituitary
✓	Duodenum	✓	Spleen	✓	Eyes (optic n.)
✓	Jejunum	✓	Thymus		**GLANDULAR**
✓	Ileum			✓	Adrenal gland
✓	Cecum		**UROGENITAL**	✓	Lacrimal/Harderian glands
✓	Colon	✓	Kidneys	✓	Mammary gland
✓	Rectum	✓	Urinary bladder	✓	Parathyroids
✓✓	Liver	✓	Testes	✓	Thyroids
✓	Gall bladder	✓	Epididymides		Auditory sebaceous glands
✓	Pancreas	✓	Prostate	✓	Coagulating glands
	RESPIRATORY	✓	Seminal vesicle		**OTHER**
✓	Trachea	✓	Ovaries and oviducts	✓	Bone
✓	Lung	✓	Uterus	✓	Skeletal muscle
✓	Nasal tissues	✓	Cervix	✓	Skin
	Pharynx	✓	Vagina	✓	All gross lesions and masses
✓	Larynx				

The (✓) tissues were examined from all animals in the control and 1000 mg/kg bw/day groups, and all animals that died or were sacrificed in a moribund condition. In addition, liver, lungs, kidneys and relevant gross lesions were examined for all animals in the 50, 2500 and 500 mg/kg bw/day groups.

II. RESULTS

A. Observations:

1. Mortality: The mortality rates at the end of the study were 38, 32, 34, and 42% for males in the control, 50, 250, and 1000 mg/kg bw/day groups, respectively, and 16, 34, 30, and 42% for females in the control, 50, 250, and 1000 mg/kg bw/day groups, respectively. The incidence of mortality in females given 50 or 1000 mg/kg/day was statistically identified as increased, relative to controls. There were no

statistically identified differences in the incidence of mortality in females given 250 mg/kg/day, nor in males at any dose level. The most common cause of death in high-dose females was nephropathy. However, the overall incidence and severity of nephropathy was not increased in males or females from any dose group. Therefore, the increased number of high-dose females that died or were euthanized moribund was interpreted to be unrelated to treatment. The statistically identified increase in mortality of females given 50 mg/kg bw/day was interpreted to not be treatment related because of the lack of a dose response, and the absence of any treatment-related histopathologic effects at this dose level.

Table 2 - Mortality Incidence and Survival Rates for Male and Female Mice[a]

	Dose (mg/kg bw/day)			
	0	**50**	**250**	**1000**
Mortality, Sacrificed: Males	6	7	7	10
Females	3	10	7	10
Mortality, Found dead: Males	13	8	10	11
Females	5	7	8	10
Mortality, Accidental: Males	0	1	0	0
Females	0	0	0	1
Survival rate, at 12 months: Males	88%	86%	84%	82%
Females	98%	90%	94%	90%
Survival rate, at 18 months: Males	62%	68%	66%	58%
Females	84%	66%*	70%	58%*

[a] Data extracted from pages 85, 86 and 512 to 1416 of the study report, and from the individual animal data; n=50.
* Statistically significantly different from control, $p<0.05$.

2. Clinical Observations: There were no overt, clinical signs of treatment-related toxicity.

B. Body Weight: There was no treatment-related effect on body weight or body weight gain.

C. Food Consumption and Compound Intake:

1. Food Consumption: There were no treatment-related findings.

2. Compound Consumption (time-weighted average): Based on food consumption, the nominal dietary concentrations and body weight, the doses expressed as mean daily mg test substance/kg body weight during the study period are presented in Table 1.

3. Food Efficiency: Calculated feed efficiencies were highly variable within and between dose levels and were likely a reflection of the normal variability in feed consumption and body weight gain. There were no treatment-related effects on feed efficiency.

D. Ophthalmoscopic Examination: There were no treatment-related findings.

E. Blood Analyses:

1. Hematology: There were no treatment-related findings.

2. Clinical Chemistry: Not conducted.

F. Urinalysis: Not conducted.

G. Sacrifice and Pathology:

1. Organ Weight:
Males: There were no treatment-related findings.

Females: Refer to Tables 3 and 4. There were no treatment-related findings in organ weights of male or female mice at any dose level tested. The only statistically identified alterations in organ weights were elevated mean absolute and relative ovary weights of mice given 50 or 250 mg/kg bw/day. The elevated ovary weights from these dose levels were reflective of an increase in the incidence of individual animals with grossly observed fluid-filled ovarian cysts. These cysts were recorded as dilatation of the ovarian bursa or as hematocysts at gross necropsy, and were not drained prior to weighing so that the structural integrity of the ovaries was maintained for histological examination. Microscopic evaluation of the ovaries from all females revealed no treatment-related increases in the number of animals with ovarian cysts or hematocysts. The mean absolute and relative ovary weights of mice given 1000 mg/kg bw/day were also higher than controls, but not statistically identified. The elevated mean ovary weights of mice given 1000 mg/kg/day were reflective of one female with markedly distended fluid-filled cysts of both ovaries. If the ovary weight (6.798 grams) of this individual animal was excluded from statistical analysis, the mean absolute and relative ovary weights of mice given 1000 mg/kg bw/day would have been comparable (0.119 grams) to the controls. The alterations in ovary weights were interpreted to not be treatment related because of the lack of a dose response, and the absence of any histopathologic ovarian effects. The higher mean ovarian weights in the 50 and 250 mg/kg bw/day groups were interpreted to be reflective of the variability in the size of ovarian cysts or hematocysts. If the ovarian weights of animals from the scheduled terminal necropsy that had grossly observed dilatation of the ovarian bursa or hematocysts were excluded from analysis, the ovarian weights of all dose levels were comparable to controls.

TABLE 3 - Ovary Weights, all ovaries[a], absolute (g) and relative to bw (g/100 g)

	Dose (mg/kg bw/day)			
	0 (n=42)	**50 (n=33)**	**250 (n=35)**	**1000 (n=29)**
Ovaries - absolute	0.161±0.342	0.236±0.279*	0.359±0.566*	0.349±1.259
- relative	0.438±0.938	0.628±0.734*	0.976±1.611*	0.886±3.055

[a] Data obtained from page 115 in the study report.
* Statistically significantly different from control, $p<0.05$.

TABLE 4 - Ovary Weights, excluding animals with dilated ovarian bursa or hematocyst[a], absolute (g) and relative to bw (g/100 g)

	Dose (mg/kg bw/day)			
	0 (n=33)	50 (n=15)	250 (n=16)	1000 (n=22)
Ovaries - absolute	0.043±0.030	0.052±0.054	0.049±0.027	0.047±0.058
- relative	0.116±0.077	0.136±0.143	0.128±0.069	0.123±0.148

[a] Data obtained from page 116 in the study report.
* Statistically significantly different from control, $p<0.05$.

2. Gross Pathology:
Males: There were no treatment-related findings.

Females: Refer to Table 5. In the 1000 mg/kg bw/day, there was an increased incidence of pale kidneys. Most of the animals with pale kidneys had moderate or severe nephropathy. Other gross observations that were more frequent in females given 1000 mg/kg bw/day consisted of decreased amount of body fat, the presence of hemolyzed blood in the gastrointestinal tract, pulmonary atelectasis and perineal soiling. These gross observations were interpreted to reflect debility and/or stress of the animals that died spontaneously or were euthanized moribund, and not primary treatment-related alterations. Females given 50, 250 or 1000 mg/kg bw/day had an increased incidence of dilatation of the ovarian bursa. Microscopic evaluation of the ovaries revealed that most of the fluid-filled ovarian structures were not dilated bursas, but rather, were ovarian cysts derived from anovulatory follicles, or from epithelial cords of the interstitium of the ovary. The increased incidence of dilatation of the ovarian bursa in females given 50, 250 or 1000 mg/kg bw/day was interpreted to not be treatment-related because of the lack of a dose response, and the absence of any histopathologic ovarian effects. Ovarian cysts are a common spontaneous alteration in aging female mice.

TABLE 5 - Selected Gross Pathological Findings

	Dose (mg/kg bw/day)			
Finding	0	50	250	1000
Kidneys, pale; bilateral	5	6	7	13
Decreased body fat	4	5	8	9
Hemolyzed blood in GIT	1	5	1	10
Atelectesis	0	0	2	4
Perineal soiling	2	5	3	8
dilatation, Ovarian Bursa, any Symmetry	11	25	27	16

[a] Data obtained from pages 118 to 134 in the study report; n=50.

3. Microscopic Pathology:

a) Non-neoplastic: There were no treatment-related statistically identified histopathologic effects in males or females at any dose level. The overall incidence of nephropathy in treated mice from all modes of death (spontaneous death, moribund, and scheduled terminal sacrifice) was comparable to controls at all dose levels. However, in females given 1000 mg/kg bw/day (high-dose) that died spontaneously or were euthanized moribund, there was an increased incidence of moderate or severe nephropathy as a contributory factor of their deaths. There were 11 mice of early death or moribund status with

nephropathy at the 1000 mg/kg bw/day dose level, versus 4, 2, and 4 mice of early death or moribund status with nephropathy at the 0, 50, or 250 mg/kg bw/day dose levels, respectively. The increased incidence of moderate or severe nephropathy in high-dose females that died or were euthanized moribund was interpreted to be unrelated to treatment, because the overall incidence and severity of nephropathy was not increased in males or females from any dose group. Spontaneous nephropathy is a common age-related degenerative alteration of mice.

b) Neoplastic: Refer to Table 6. There was an increased incidence of bronchiolo-alveolar carcinoma in the lungs in the 1000 mg/kg bw/day group, males only. Historical control data for this tumor type indicated that the incidence observed in this study was within the normal range. Thus the slight increased in bronchiolo-alveolar tumors in the high-dose males was not considered to be treatment related.
There were no other differences between treated animals and controls in the number of tumor bearing mice (benign and/or malignant) or the incidence of any specific tumor type in any organ.

TABLE 6 - Incidence of Pulmonary Bronchiolo-Alveolar Tumors in Male Mice[a]

	Dose (mg/kg bw/day)			
	0	50	250	1000
Adenoma; primary, incidental	9	11	9	6
Adenoma; two, primary, incidental	0	0	0	1
Adenoma; three, primary, incidental	0	1	0	1
Carcinoma; malignant with metastasis, primary, fatal	0	0	0	1
Carcinoma; malignant without metastasis, primary, incidental	2	1	2	5

[a] Data obtained from page 150 in the study report; n=50.

III. DISCUSSION

A. Investigators' Conclusions: "There were no treatment-related effects in males at any dose level. Females given 1000 mg/kg/day (high-dose) had a statistically identified increase in mortality which was interpreted to be treatment related. The most common cause of death in high-dose females was nephropathy. However, the overall incidence and severity of nephropathy was not increased in males or females from any dose group. Therefore, the increased number of high-dose females that died or were euthanized moribund due to nephropathy was interpreted to be unrelated to treatment. There were no other treatment-related effects in females at any dose level. No increase in neoplasms was observed in either male or female mice at any dose level indicating that XDE-750 did not have an oncogenic potential under the conditions of this study. The NOEL for males was 1000 mg/kg/day and for females was 250 mg/kg/day."

B. Reviewer Comments: Male and female CD-1 mice were fed test diets containing technical XDE-750, purity 94.5%, at dose levels of 0, 50, 250 or 1000 mg/kg bw/day (equal to 0, 50.2, 251 or 1000 mg/kg bw/day for males, and 0, 50.9, 252 or 1010 mg/kg bw/day for females) for up to 18 weeks, 50 mice/sex/group.
There were no treatment-related effects on mortality, clinical signs, ophthalmology, body weight/body weight gain, food intake, food efficiency, hematology, organ weights, gross pathology or

histopathological examination. The only oncogenic finding was an increased incidence of pulmonary bronchiolo-alveolar carcinomas in the 1000 mg/kg bw/day group, males only. Historical control data for this tumor type indicated that the incidence observed in this study was within the normal range. Thus the slight increased in bronchiolo-alveolar tumors in the high-dose males was not considered to be treatment related.

The systemic LOAEL could not be determined since there were no adverse, treatment-related findings observed at any dose level tested. The NOAEL was 1000 mg/kg bw/day (equal to 1000 mg/kg bw/day for males and 1010 mg/kg bw/day for females).

C. Study Deficiencies: No scientific deficiencies were noted in the study.